PATENT SPECIFICATION (11) 1 269 551

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NO DRAWINGS

(21) Application No. 16116/69 (22) Filed 27 March 1969

(23) Complete Specification filed 12 March 1970

(45) Complete Specification published 6 April 1972

(51) International Classification C 07 c 101/00; C 07 d 9/00, 41/00, 67/00, 93/42; A 61 k 27/00

(52) Index at acceptance

C2C 171—178—185 171—179—180 174—177—181 179—194—273 182—194—277 185—191—277 1E5K4 1E6K4 1Q11J 1Q4 1Q6C 1Q8A 1Q9F2 213 227 22X 22Y 247 253 254 256 25Y 292 29X 29Y 30Y 311 313 31Y 322 323 32Y 337 338 357 366 367 368 440 456 45Y 490 620 628 658 65X 660 670 680 698 69Y 790 79Y LT LZ ZH

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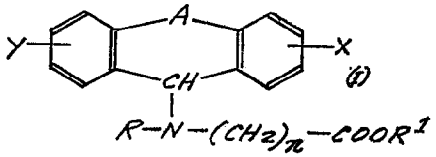
(54) NEW TRICYCLIC DERIVATIVES AND PROCESS FOR THEIR MANUFACTURE

(71) We, SCIENCE UNION ET CIE, Societe Francaise de Recherche Medicale, a Body Corporate organised according to the laws of France, of 14 Rue du Val d'Or, Suresnes 92, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention provides tricyclic derivatives of general formula (I):



(I)

wherein A represents a bridge selected from the following radicals:

$-(CH_2)_m-$, $-CH=CH-$, $-(CH_2)_p-O-$, $-(CH_2)_p-S-$, $-(CH_2)_p-SO_2-$, $-(CH_2)_p-NR_1-$ and $-SO_2-NR_2-$,

in which m has the value 1, 2 or 3, p has the value 1 or 2, R_1 represents a hydrogen atom or a lower alkyl radical containing 1 to 5 carbon atoms, and R_2 represents a lower alkyl radical containing 1 to 5 carbon atoms, X and Y may be the same or different and each represents a hydrogen atom or a halogen atom, for example a fluorine, chlorine or bromine atom, R and R′ may be the same or different and each represents a hydrogen atom or a lower alkyl radical containing 1 to 5 carbon atoms in a straight or branched chain and n is an integer of from 1 to 12 inclusive.

The derivatives of general formula (I) in which R′ represents a hydrogen atom are amphoteric compounds which yield metal salts with bases of the alkali or alkaline earth metals, for example sodium, potassium of calcium hydroxide, carbonate and bicarbonate, and salts with inorganic or organic acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, propionic, maleic, fumaric, methanesulphonic, tartaric, citric oxalic and benzoic acid. The derivatives of general formula (I) in which R′ represents an alkyl radical are basic compounds which yield salts with inorganic or organic acids mentioned above. All these salts are included in the present invention.

Furthermore, some derivatives of general formula (I) possess an asymmetric carbon atom and thus exist in the form of optical isomers. These optical isomers are included in the present invention.

The present invention also provides a process for preparing the derivatives of the general formula (I) which comprises condensing a halogenated derivative of general formula (II):

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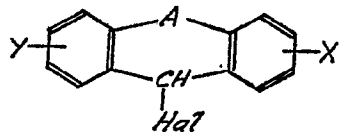


(II)

in which A, X and Y have the meanings given above and Hal represents a chlorine or bromine atom, with an ω-amino-alkanoic acid ester of general formula (III):

$$R—NH—(CH_2)_n—COOR' \qquad (III)$$

in which R and *n* have the values given above and R′ represents a lower alkyl radical containing 1 to 5 carbon atoms, so as to yield the derivatives of general formula (I) in which R′ is a lower alkyl radical, and then optionally saponifying the ester so obtained to yield a derivative of general formula (I) in which R′ is a hydrogen atom.

The condensation may be carried out in a suitable organic solvent, for example nitromethane, acetonitrile or dimethylformamide, in the presence of an acceptor for the hydrohalic acid formed during the reaction. This acceptor may be an excess of the ω-amino-alkanoic acid ester (III), a tertiary aliphatic amine, a pyridine base, or an alkali or alkaline earth metal carbonate or bicarbonate. The reaction is generally slightly exothermic and takes place at a temperature preferably within the range of from 20 to 100°C.

The saponification of the resulting ester is preferably carried out either in an alkaline aqueous alcoholic medium or in a strongly acid aqueous alcoholic medium.

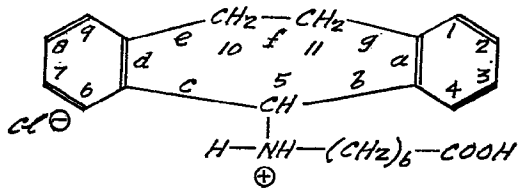
The halogenated starting derivatives (II) have been prepared by methods which are in themselves known, starting from the corresponding hydroxylated derivatives, which are either treated with dry hydrochloric acid or with thionyl chloride. These hydroxylated derivatives are themselves prepared from the corresponding ketones, the majority of which are known derivatives.

The physical constants of the new starting materials, whether they be ketones, alcohols or halides, are given in the Examples which follow.

The following Examples illustrate the invention. The melting points are, unless otherwise stated, determined on a Kofler block. They are in fact decomposition points, the determination of which is rather imprecise.

EXAMPLE 1

7-[dibenzo (a,d) cycloheptadien-5-yl] aminoheptanoic acid hydrochloride



6.5 g of 5-chloro-10, 11-dihydro-5H-dibenzo (a,d)-cycloheptene in 60 ml of nitromethane and 10.8 g of ethyl 7-aminoheptanoate in 12 ml of nitromethane were mixed at ambient temperature. The reaction was slightly exothermic. The reaction mixture was left to stand overnight and the solvent was evaporated *in vacuo*. The residue was taken up in normal hydrochloric acid and the resulting precipitate was filtered off.

10.5 g of crude ethyl 7-[dibenzo (a,d) cycloheptadien-5-yl] amino-heptanoate hydrochloride were obtained, of which a sample recrystallised from benzene gave a pure product melting instantaneously at 166 to 168°C.

The hydrochloride of the crude ester obtained above was added to 25 ml of 2N hydrochloric acid. The whole was kept under reflux for 2 hours. The material dissolved and a new hydrochloride then reprecipitated. After cooling, the hydrochloride of the crude acid was filtered off, washed with iced water and then recrystallised from distilled water. 5.7 g of 7-[dibenzo (a,d) cycloheptadien-5-yl] amino-heptanoic acid hydrochloride were obtained, melting instantaneously at 226 to 230°C.

EXAMPLES 2—11

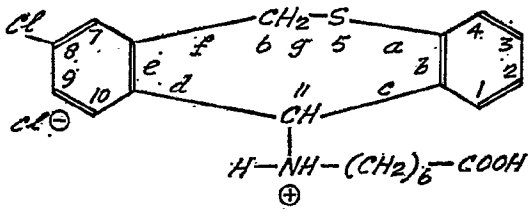
The derivatives, of which substituents and melting points are collected together in the Table below, were prepared according to the process described in Example 1:

TABLE 1

Ex.	A	X	Y	R	R′	n	Form isolated	Instantaneous melting point
2	$-CH_2-CH_2-$	H	H	H	H	5	hydrochloride	210 °C
3	— „ —	H	H	H	H	7	— „ —	180 — 185 °C
4	— „ —	H	H	H	H	10	— „ —	142 — 144 °C
5	— „ —	Cl—2	H	H	H	6	— „ —	180 °C
6	— „ —	Cl—3	H	H	H	6	— „ —	210 °C
7	$-CH_2-CH_2-CH_2-$	H	H	H	H	6	— „ —	>260 °C
8	—CH = CH—	H	H	H	H	5	free acid	120 °C
9	—CH = CH—	H	H	H	C_2H_5	6	hydrochloride	158 — 160 °C
10	— „ —	H	H	H	C_2H_5	7	— „ —	150 °C
11	— „ —	H	H	H	C_2H_5	10	— „ —	128 — 130 °C

EXAMPLE 12

dl-7-[8-chloro-dibenzo (b,e) thiepin-11-yl] aminoheptanoic acid hydrochloride



2 g of 4-chloro (α-phenylthio) toluic acid were added to a solution of 7.2 g of phosphorus pentoxide, P_2O_5, in 5 ml of phosphoric acid. The reaction mixture was kept at 100°C. for 2 hours whilst stirring. It was decomposed with ice and then extracted with benzene. The benzene phase was washed with dilute sodium hydroxide solution and then with water, dried and evaporated. The residue was recrystallised from cyclohexane. 1 g of 8-chloro-dibenzo (b,e) thiepin-11-one, melting (micro-Kofler) at 152—153°C., was obtained.

4.5 g of 8-chloro-dibenzo (b,e) thiepin-11-one in 50 ml of methanol were treated with 1.31 g of sodium borohydride. After the usual treatment, 4 g of the crude corresponding alcohol, melting point 110—115°C., were obtained. After recrystallisation from aqueous ethanol, 3.2 g of 8-chloro-dibenzo (b,e) thiepin-11-ol, melting at 115—117°C., were obtained.

2.8 g of 8-chloro-dibenzo (b,e) thiepin-11-ol were added to 50 ml of thionyl chloride. The mixture was kept under reflux for 1 hour and the excess of reagent was then evaporated *in vacuo*. The crystalline residue was recrystallised from cyclohexane. 2 g of 8,11-dichloro-dibenzo (b,e) thiepine, melting at 121—123°C., were obtained.

7.2 g of 8,11-dichloro-dibenzo (b,e) thiepine were reacted with 9 g of ethyl 7-aminoheptanoate in nitromethane in accordance with the process described in Example 1. 10.9 g of a product containing 99% of ethyl 7-[8-chloro-dibenzo (b.e.) thiepin-11-yl] aminoheptanoate were finally obtained in the form of a non-crystalline gum. 9.9 g of this ester were treated with 60 ml of normal hydrochloric acid and refluxing was continued for 2 hours. The whole was evaporated *in vacuo*. The residue was taken up in 50 ml of acetonitrile. The whole was heated under reflux, and then filtered whilst hot. The filtered and dried product was then recrystallised from distilled water. 6 g of *dl*-7-[8-chloro-dibenzo (b,e)-thiepin-11-yl] amino-heptanoic acid hydrochloride, melting instantaneously at 200—210°C., were obtained.

EXAMPLES 13—27

The derivatives, of which the substituents and melting points are collected together in the Table below, were prepared according to the process described in Example 12. This Table also contains the melting points of the starting materials used where these are new products:

TABLE 2

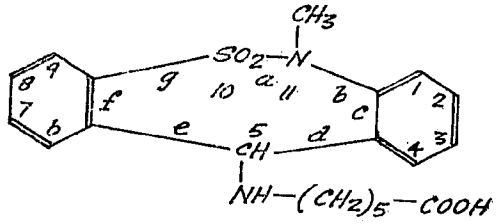
Ex.	A	X	Y	R	R′	n	form isolated	instanyaneous melting point	melting point of the corresponding chlorinated derivative	melting point of the corresponding hydroxyl derivative
13	—CH_2—O—	H	H	H	C_2H_5	5	hydrochloride	180 °C	not isolated in the pure state	—
14	— „ —	Cl—2	H	H	H	6	— „ —	204 °C	122 — 126 °C	138 — 140 °C
15	— „ —	Cl—3	H	H	H	6	— „ —	190 °C	80 — 84 °C	113 — 115 °C
16	— „ —	F—2	H	H	H	6	— „ —	206 °C	154 — 158 °C	76 — 78 °C
17	— „ —	H	Cl—8	H	H	6	— „ —	180 °C	110 — 115 °C	104 — 108 °C
18	—CH_2—S—	Cl—3	H	CH_3	H	5	free acid	140 — 142 °C	not isolated in the pure state	—
19	— „ —	Cl—3	H	H	H	6	hydrochloride	210 °C	— „ —	—
20	— „ —	Cl—3	Cl—9	H	H	6	— „ —	210 °C	100 — 102 °C	160 — 162 °C
21	— „ —	Cl—2	H	H	H	5	— „ —	200 — 203 °C	104 — 106 °C	158 — 160 °C
22	— „ —	Cl—3	H	H	H	5	— „ —	181 — 182 °C	not isolated in the pure state	140 — 142 °C

TABLE 2—cont.

Ex.	A	X	Y	R	R'	n	form isolated	instantaneous melting point	melting point of the corresponding chlorinated derivative	melting point of the corresponding hydroxyl derivative
23	$-CH_2-S-$	Cl—2	H	H	H	6	hydrochloride	—	—	—
24	— „ —	Cl—3	H	H	H	6	— „ —	200°C	—	—
25	$-CH_2-SO_2$	Cl—3	H	H	H	5	— „ —	206°C	—	—
26	$-CH_2-CH_2-S-$	H	H	H	H	5	— „ —	210 — 212°C	—	—
27	— „ —	H	H	H	H	6	— „ —	247 — 248°C	—	—

EXAMPLE 28

dl-6-[10,10-dioxo-11-methyl dibenzo (c,f) thiazepin (1,2)-5-yl]-aminohexanoic acid



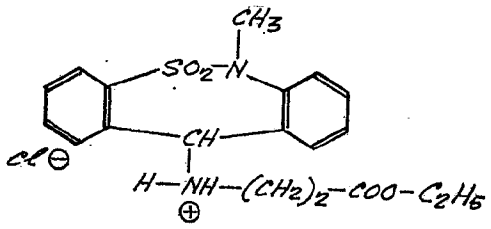
A solution of 8 g (0.05 mol) of freshly distilled ethyl 6-aminocaproate in 10 ml of nitromethane were added all at once to a well-stirred suspension of 7.3 g (0.025 mol) of 5-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepine-(1,2) in 40 ml of distilled nitromethane. A slight exothermic reaction was observed with the temperature rising to 35°C. and the halogenated derivative dissolving completely. Stirring was then continued for 30 minutes. The reaction mixture was evaporated *in vacuo*. The residue was taken up in 30 ml of water. The insoluble oil which separated out was extracted with benzene and the benzene phase was washed with water and then dried over sodium sulphate. The solvent was evaporated *in vacuo* and 10.7 g of crude oily ethyl *dl* 6-[10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] aminohexanoate

were obtained, in which the content of pure product determined by measurement with perchloric acid in an acetic acid medium is 95%.

10.4 g of this ester thus obtained were treated with 1 g of sodium hydroxide dissolved in 60 ml of ethanol and 10 ml of water. The mixture was kept under reflux for 45 minutes and then evaporated *in vacuo*. The residue was taken up in 30 ml of water and the aqueous solution was extracted with ether. The aqueous phase was cautiously acidified to pH 4.5—5. The acid which precipitated was extracted with chloroform. The chloroform phase was washed and dried, and then evaporated. The 7.3 g of crude acid thus obtained was recrystallised from 10 ml of ethanol and 5.5 g of *dl*-6-[10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] amino-hexanoic acid were thus obtained, melting instantaneously at 118°C.

EXAMPLE 29

Ethyl dl-3-[10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] aminopropionate hydrochloride

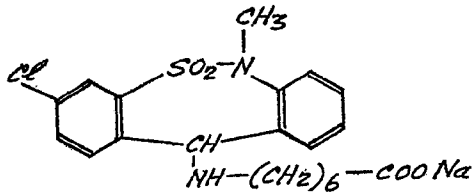


Working as in Example 28 and starting from 11.6 g of 5-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2) and 9.4 g of ethyl β-aminopropionate, 15 g of *dl*-3-[10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] aminopropionate were obtained, containing 94% of pure product as determined by measurement with perchloric acid.

15 g of this crude ester were dissolved in 150 ml of anhydrous ether and treated with a solution of hydrochloric acid in anhydrous ether. The hydrochloride precipitated and was filtered off, washed with ether and dried. 15.5 g of crude ethyl *dl*-3-[10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] aminopropionate hydrochloride were obtained, which on recrystallisation from water yielded 12.3 g of a pure product, melting instantaneously at 210°C.

EXAMPLE 30

Sodium 7-[8-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] amino-heptanoate



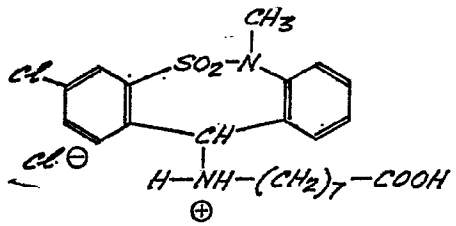
A solution of 27.6 g (0.16 mol) of freshly distilled ethyl 7-aminoheptanoate in 40 ml of nitromethane was added all at once and with mechanical stirring to a suspension of 26.2 g (0.08 mol) of 5,8-dichloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepine-(1,2) in 120 ml of nitromethane. The whole was heated to 55°C. for 30 minutes, the solvent was then evaporated *in vacuo* and the residue was taken up in water. The crude ester was extracted with ether. After evaporation of the ether 36 g of crude ester were obtained, and 30 g (0.065 mol) thereof were treated under reflux with a solution of 2.8 g (0.07 mol) of sodium hydroxide in 75 ml of ethanol and 25 ml of water. After one hour's refluxing, the alcohol was evaporated *in vacuo*. The residue was taken up in 150 ml of water. The mixture was twice extracted with 75 ml of chloroform and the aqueous phase was evaporated *in vacuo*. The sodium salt was then dissolved in 150 ml of chloroform, the solution was dried over sodium sulphate and the product precipitated with anhydrous ether.

The salt was filtered off, washed with ether and dried at 50°C. 13 g of sodium

7-[8-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] amino-heptanoate, melting with decomposition at about 180°C., were obtained.

EXAMPLE 31

dl-8-[8-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin (1,2)-5-yl] amino-octanoic acid hydrochloride



9.35 g (0.050 mol) of freshly prepared ethyl 8-aminooctanoate were added all at once and while stirring to a suspension of 8.2 g (0.025 mol) of 5,8-dichloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepine-(1,2) in 60 ml of nitromethane. The whole was kept at 45—50°C. for 20 minutes, the solvent was then evaporated *in vacuo* and the crude ester was extracted as in the preceding Examples.

The crude ester was added to 25 ml of 2N hydrochloric acid and the mixture is boiled for 1 hour, and evaporated to dryness *in vacuo*. The residue was recrystallised from 75 ml of acetonitrile and 7 g of *dl*-8-[8-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] aminooctanoic acid hydrochloride, melting instantaneously at 188—190°C., were obtained.

EXAMPLES 32—44

The derivatives, of which the substituents and melting points were collected in the Table below, were prepared according to the process described in Examples 28 to 31. The 5-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepines-(1,2) which are the starting materials used in Examples 28 to 44 are described in our French Patent Specification No. 1,566,191.

TABLE 3

Ex.	A	X	Y	R	R′	n	form isolated	instantaneous melting point
32	$-SO_2-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{N}}-$	H	H	H	H	1	free acid	200 °C
33	— „ —	H	H	H	C_2H_5	1	hydrochloride hemihydrate	180 °C
34	— „ —	H	H	CH_3	Na	3	dihydrate	150 °C
35	— „ —	Cl—2	H	H	H	5	free acid hemihydrate	115 °C
36	— „ —	Cl—3	H	H	H	5	hydrochloride	210 °C
37	— „ —	H	Cl—8	H	H	5	free acid	50 — 70 °C
38	— „ —	Cl—2	Cl—8	H	H	5	hydrochloride dihydrate	150 °C
39	— „ —	H	Cl—8	H	Na	5	sodium salt hemihydrate	
40	— „ —	H	Cl—7	H	Na	5	sodium salt tetrahydrate	160 °C
41	— „ —	Cl—3	Cl—8	H	Na	5	sodium salt	170 °C
42	— „ —	H	Cl—8	CH_3	H	5	free acid	130 °C
43	— „ —	H	Cl—8	H	Na	10	sodium salt	254 °C
44	— „ —	H	F—8	H	H	6	free acid	

The new tricyclic compounds and their physiologically tolerable salts possess valuable pharmacological and therapeutic properties, especially psychostimulant, antidepressive, analgesic, antitussive, antihistaminic and gastric antisecretory properties.

Their toxicity is low and the LD_{50} studied in mice varies from 150 to > 1000 mg/kg by the intraperitoneal route and from 200 to > 1200 mg/kg by the oral route.

The stimulant activity on the central nervous system was demonstrated by actography in mice. Administered at doses of 5 to 40 mg/kg, the new compounds increase the number of movings of the animals from 4 to 10 times compared with the untreated animals 2 hours after the administration by subcutaneous, intraperitoneal or oral route. By the same test it was observed that the compounds of the invention antagonise the depressive effects of reserpine at doses of 25 to 50 mg/kg.

The analgesic activity was studied by the method of Woolf G. and MacDonald A.D. [J. Pharm. *80*, 300 (1944)]. It was found that the compounds of the invention, administered in mice by intraperitoneal route as doses of 5 to 20 mg/kg, increase the threshold of pain perception from 30 to 170%.

The antitussive activity was studied by the method of Gooswald R. [Arzfschg *8*, 550 (1958)]. The new compounds, administered by subcutaneous route in a guinea-pig at doses of 2 to 20 mg/kg, decrease from 40 to 90% the cough of the animals submitted to a 40% citric acid aerosol for 4 minutes.

The new compounds inhibit the bronchospasm provoked by intravenous injection of histamine in a guinea-pig [Konzett and Rossler: Arch. Exp. Path. U. Phar. *195*, 71 (1940)]. The spasm is inhibited from 26 to 75% by intravenous doses of 2.5 to 5 γg/kg.

The gastric antisecretory activity was studied by the method of H. Shay et al. [Gastroenterology *5*, 43 (1945)]. It was observed that the new compounds inhibit the gastric secretion in a rat at doses of 5 to 50 mg/kg by intraperitoneal route. The decrease of the volume of gastric secretion in treated animals varies from 20 to 70% compared with the untreated animals 4 hours after the ligature of pylorus.

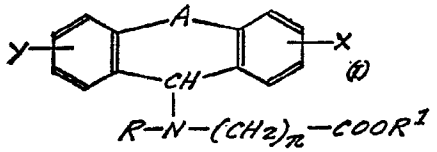
The properties described above, as well as the low toxicity, allow the use of the new compounds in therapy, especially in the treatment of psychoneurotic disorders, pain, cough and gastric hypersecretion.

The present invention also provides pharmaceutical compositions, which are especially suitable for oral, rectal or parenteral administration, comprising, as active ingredient, a compound of the general formula (I) or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier, for example distilled water, glucose, lactose, talc, starch, magnesium stearate and cocoa butter.

Doses of the active ingredient may vary from 10 to 100 mg, 1 to 5 times a day.

WHAT WE CLAIM IS:—

1. Tricyclic derivatives of the general formula (I)



wherein A represents a bridge selected from the following radicals

$-(CH_2)_m-$, $-CH=CH-$, $-(CH_2)_p-O-$, $-(CH_2)_p-S-$, $-(CH_2)_p-SO_2-$, $(CH_2)_p-NR_1-$ and $-SO_2-NR_2-$,

in which m has the value 1, 2 or 3, p has the value 1 or 2, R_1 represents a hydrogen atom or a lower alkyl radical containing 1 to 5 carbon atoms, and R_2 represents a lower alkyl radical containing 1 to 5 carbon atoms, X and Y are the same or different and each represents a hydrogen atom or a halogen atom, R and R′ are the same or different and each represents a hydrogen atom or a lower alkyl radical containing 1 to 5 carbon atoms in a straight or branched chain and n is an integer of from 1 to 12 inclusive.

2. Tricyclic derivatives as claimed in claim 1, wherein X and Y each represents a fluorine, chlorine or bromine atom.

3. Salts of a derivative of the general formula (I), wherein R′ is a hydrogen atom, with a suitable base or acid.

4. Salts of a derivative of the general formula (I), wherein R′ is a lower alkyl radical, with a suitable inorganic or organic acid.

5. 7-[dibenzo (a,d) cycloheptadien-5-yl] aminoheptanoic acid.

6. 7-[dibenzo (a,d) cyclooctadien-5-yl] aminoheptanoic acid.

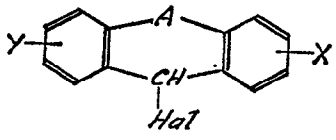
7. Ethyl 11-[dibenzo (a,d) cycloheptatrien-5-yl] aminoundecanoate.

8. *dl*-7-[8-chloro-dibenzo (b,e) thiepin-11-yl] aminoheptanoic acid.

9. *dl*-7-[2-fluoro-dibenzo (b,e) oxepin-11-yl] aminoheptanoic acid.

10. Sodium 7-[8-chloro-10,10-dioxo-11-methyl-dibenzo (c,f) thiazepin-(1,2)-5-yl] aminoheptanate.

11. A process for preparing the derivatives claimed in claim 1, wherein a halogenated derivative of the general formula (II)



(II)

wherein A, X and Y have the meanings given in claim 1 and Hal represents a chlorine or bromine atom, is condensed with an ω-amino-alkanoic acid ester of the general formula (III)

$$R—NH—(CH_2)_n—COOR' \qquad (III)$$

wherein R and *n* have the meanings given in claim 1 and R′ is a lower alkyl radical containing from 1 to 5 carbon atoms, in order to obtain the derivatives of the general formula (I), wherein R′ is a lower alkyl radical, and then optionally saponifying the ester so obtained to yield the derivatives of the general formula (I) wherein R′ is a hydrogen atom.

12. A process as claimed in claim 11, wherein the condensation of the derivatives (II) and (III) is carried out in an organic solvent, in the presence of an acceptor for the hydrohalic acid formed during the reaction, at a temperature within the range of from 20 to 100°C.

13. A process as claimed in claim 11, wherein the saponification of the resulting ester is carried out either in an alkaline aqueous alcoholic medium or in a strongly acid aqueous alcoholic medium.

14. A process as claimed in claim 11, conducted substantially as described in any one of the Examples herein.

15. A compound as claimed in claim 1, whenever prepared by a process claimed in any one of claims 11 to 14.

16. A pharmaceutical preparation which comprises as active ingredient a derivative as claimed in any one of claims 1, 2 and 5 to 10 or a physiologically tolerable salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

17. A pharmaceutical preparation as claimed in claim 16, in dosage unit form, which contains within the range of from 10 to 100 mg of the active ingredient.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.